REMARKS

Applicants gratefully acknowledge the Examiner's statement that Claims 1-3, 6, 8-23 and 39 are free of the prior art.

I. The Amendments

The claims have been amended, without prejudice, to more particularly describe the claimed invention and to expedite prosecution. The amendments do not add new matter and are fully supported in the Specification. In particular, Claims 1-3 and 6-23 have been canceled, without prejudice, and replaced with new Claims 46-50, 52-63, 65-73, 77, 79-83 and 85-90 in order to better group related claims and to describe the invention with greater particularity. The following chart shows the correspondence between these new claims and the previously pending claims.

Previously Pending Claim	New Claim(s)
1	46
2	47
3	48
6	58
7	72, 73
8	77
9	79
10	80
11	81
12	59
13	60
14	61
15	71
16	49, 62, 82
17	50, 63, 83
18	52, 65, 85
19	53, 66, 86
20	54, 67, 87
21	55, 68, 88
22	56, 69, 89
23	57, 70, 90
39	39

Each of the new claims listed in the above chart is supported, for example, by the corresponding previously pending claim as it was originally filed. Claim 46 is further supported in the Specification at, for example, page 5, lines 9 and 10 and page 8, lines 5 and 6. Claim 58 is further supported in the Specification at, for example, page 5, lines 22-35 and at page 9, lines 11-20. Claim 72 is further supported in the Specification at, for example, page 5, lines 22-35. Claim 77 is further supported in

the Specification at, for example, page 5, lines 22-35. Claim 79 is further supported in the Specification at, for example, page 5, lines 22-35.

Claims 51, 64, 74-76, 78 and 84 also have been added. Claims 51, 64, and 84 are supported in the Specification at, for example, page 16, lines 1-2. Claims 74-76 and 78 are supported in the Specification at, for example, page 8, lines 5-27. Claim 78 is further supported in the Specification at, for example, page 5, line 32 through page 7, line 35.

The amendment to Claim 39 is supported in the Specification at, for example, page 5, lines 9 and 10 and 22-35 and at page 9, lines 11-20.

Thus, the new claims and amendments do not add new matter and are fully supported in the Specification as filed. Accordingly, entry of the amendments under 35 U.S.C. § 1.111 is respectfully requested.

The claims as pending after entry of the instant amendment are attached hereto as *Appendix B.*

II. The Rejections

A. Rejection of Claims 1-3, 6, 8-23 and 39 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 6, 8-23 and 39 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Applicants respectfully point out that the instant rejection is moot with respect to canceled Claims 1-3, 6 and 8-23 and traverse with respect to new Claims 46-90.

A claim is definite if it, when "read in light of the Specification, reasonably apprise[s] those skilled in the art and [is] as precise as the subject matter permits. As a matter of law, no court can demand more." *Hybritech v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 95 (Fed. Cir. 1986). Definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *See In re Moore*, 169 USPQ 236, 238 (C.C.P.A. 1971).

It is asserted that the words "variant" and "fragment" are unclear and indefinite because the specification allegedly fails to indicate what these terms encompass. Applicants respectfully point out that the definiteness of these words must be considered in the contexts in which they appear in the claims. Claim 72, from which each of the remaining claims reciting the word "variant" or "fragment"

ultimately depends, recites in part "(a) a soluble *fragment* of the polypeptide shown as SEQ ID NO:2, wherein the *fragment* binds TWEAK; and (b) a *variant* that is at least 80% identical to (a), wherein the *variant* binds TWEAK."

The specification provides a detailed discussion of these phrases. Variants, particularly naturally occurring variants and variants of TWEAK receptor extracellular domains, are discussed at, for example, page 7, line 18 through page 8, line 27. Soluble TWEAK receptor fragments and fragments of TWEAK receptor extracellular domains capable of binding TWEAK are discussed at, for example, page 4, line 38 through page 5, line 35. Thus, the content of the application disclosure provides ample guidance to the meaning of the objected-to phrases. Consequently, the phrases in the claims comprising the terms "variant" and "fragment" are not indefinite. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

B. Rejection of Claims 1-3, 6, 8-23 and 39 Under 35 U.S.C. § 112, First Paragraph

1. Rejection of Claims 1, 6, 8, 11, 12 and 39 For Non-Enablement

Claims 1, 6, 8, 11, 12 and 39 are rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. It is asserted that the Specification is not enabling for a method of modulating angiogenesis through the administration of any antibody, fragment, variant or antagonist. Applicants respectfully point out the rejection is moot with respect to canceled Claims 1, 6, 8, 11 and 12 and traversed with respect to Claim 39 and new Claims 46-90.

A claim is enabled if a skilled artisan can practice it without *undue* experimentation. *See In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Some experimentation, even extensive experimentation, is permissible if such experimentation is routine in the art. *See In re Angstadt*, 190 USPQ 214 (C.C.P.A. 1976) ("The key word is 'undue,' not 'experimentation.'").

Applicants gratefully acknowledge the Examiner's statement that methods of inhibiting angiogenesis comprising the administration of an antagonist comprising an Fc polypeptide fusion protein comprising amino acids 28-79 of SEQ ID NO:7 or an antibody directed at the TWEAK receptor are enabled.

Claim 39, as herein amended, recites in part a method of inhibiting the binding of TWEAK to the TWEAK receptor comprising administering a composition

comprising a TWEAK receptor antagonist wherein the antagonist is selected from the group consisting of a soluble TWEAK receptor polypeptide that binds TWEAK, an antibody that binds the TWEAK receptor, an antisense nucleic acid, a triple helix forming nucleic acid, a peptide, and a small molecule. Claim 46, recites in part a method of inhibiting angiogenesis comprising administering an antagonist of a TWEAK receptor comprising a sequence as set forth from amino acids 28-79 of SEQ ID NO:7. Claim 72 recites in part a method of inhibiting angiogenesis comprising administering a therapeutically-effective amount of a composition comprising an antagonist of a TWEAK receptor, wherein the TWEAK receptor comprises a sequence as set forth from amino acids 28-79 of SEQ ID NO:7, and the antagonist comprises a polypeptide selected from the group consisting of (a) a soluble fragment of the polypeptide shown as SEQ ID NO:2, wherein the fragment binds TWEAK; and (b) a variant that is at least 80% identical to (a), wherein the variant binds TWEAK. Each of the remaining claims ultimately depends either from Claim 46 or from Claim 72.

The instant Specification provides broad and detailed directions for practicing the claimed invention. For example, the Specification teaches that the angiogenic effects of TWEAK are mediated by the TWEAK receptor and thus they can be inhibited by molecules that antagonize the TWEAK receptor. Examples of the types of molecules taught by the Specification for antagonizing the TWEAK receptor include molecules that bind the TWEAK receptor's extracellular domain (*e.g.*, an anti-TWEAK-receptor antibody; *see*, the Specification at, for example, page 9, line 5 through page 10, line 16; page 27, lines 12-30), molecules that compete with the TWEAK receptor for binding to TWEAK (*e.g.*, a soluble TWEAK receptor fragment; *see*, for example, the Specification at page 5, line 9 through page 9, line 3; page 26, line 30 through page 27, line 10) or to TRAF (*see*, for example, the Specification at p.3, lines 5-7) and inhibitory antisense, ribozyme and triple helix molecules (*see*, for example, the Specification at page 10, lines 19-27). The instant Specification further teaches how to screen molecules for anti-TWEAK receptor activity (*see, e.g.*, the Specification at, for example, page 18, line 14 through page 24, line 31; page 27, line 34 through page 28, line 12; page 28, lines 15-32 and Table 1; page 29, lines 1-28; page 29, line 30 through page 30, line 23; page 30, line 25 through page 31, line 5 and page 31, lines 7-11) and to use them to inhibit angiogenesis in a mammal (*see* the Specification at, for example, page 15, line 17 through page 18, line 11).

The Specification's detailed description of the invention is complemented by the high level of skill in the art. For example, one of skill in the art is adept at raising antibodies against a known protein target (*see, e.g., Antibodies: A Laboratory Manual*, 1988, Harlow and Lane (ed.s), Cold Spring Harbor Press), making protein and protein fragments from a known nucleic acid or protein sequence (*see, e.g., Short Protocols in Molecular Biology*, 4th ed., 1999, Ausubel *et al.* (ed.s), John Wiley & Sons), and using *in vitro* and cell-based assays to screen molecules for a biological activity with no more than routine experimentation (*see, e.g., In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) (Finding that only routine experimentation was needed to screen a collection of hybridomas for clones expressing antibodies that bind a desired target molecule).[1] Thus, one of skill in the art, guided by the disclosure of the instant Specification, can make, identify and use in the methods of the invention a large number and variety of TWEAK receptor antagonists without undue experimentation. Accordingly, the methods of the claimed invention are enabled, and Applicants respectfully request that the instant rejection be withdrawn.

2. Rejection of Claims 1-3, 6, 8-23 and 39 For Lack of Written Description

Claims 1-3, 6, 8-23 and 39 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. It is asserted that the written description of the instant Specification sets forth only the amino acid sequence of SEQ ID NO:7 and does not include naturally occurring variants and fragments. Applicants respectfully point out that the instant rejection is moot with respect to canceled Claims 1-3, 6 and 8-23 and traverse with respect to Claim 39 and new Claims 46-90.

The written description requirement is satisfied when an Applicant's disclosure conveys with reasonable clarity to one of skill in the art that, as of the filing date, the Applicant was in possession of the invention. The invention is defined by the claims. *See Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). The Examiner bears the initial burden of establishing a *prima facie* case of lack or written description by presenting evidence or reasons why one of skill in the art would not

[1] The instant Office Action states at page 4 that "[t]he art teaches TWEAK and TWEAK receptor, as it relates to apoptosis and as an inducer of angiogenesis" (citation omitted). Applicants respectfully point out that the cited reference does not teach the identity of the TWEAK receptor or its role in angiogenesis That information is provided for the first time in the instant Application.

recognize in the disclosure a description of the invention defined by the claims. *See In re Alton*, 37 USPQ2D 1578 (Fed. Cir. 1996).

To the extent that the rejection is based on the asserted lack of support for allelec variants or naturally-occurring variants, Applicants respectfully point out that it is moot as none of the claims pending after entry of the instant amendment uses these phrases.

Applicants also respectfully point out that the assertion that support is provided only for an Fc polypeptide molecule having an amino acid sequence shown in SEQ ID NO:7 is incorrect. The Specification provides both a *structural* and a *functional* description of each molecule recited in each method claim. The Specification provides, *inter alia*, the sequence of the full length TWEAK receptor and of its extracellular domain. *See* the Specification at, for example, SEQ ID NO:7 and page 4, line 39 through page 5, line 8. The Specification also states that fragments of the TWEAK receptor are part of the invention. *See* the Specification at, for example, page 5, line 9 through page 9, line 4. By disclosing the sequence of the full-length protein and stating that fragments thereof are part of the invention, the Specification allows one of skill in the art to determine the *precise* sequence of *every* fragment of the TWEAK receptor that is recited in the claims. Similarly, the Specification states that, *inter alia*, variants of the TWEAK receptor that are included in the invention comprise those that are at least 70%, 80%, 90%, *etc.* identical to the sequence in SEQ ID NO:7 and provides a method for determining the percent identity between two peptide sequences (*see* the Specification at, for example, page 8, lines 5-27), allowing one of skill in the art to determine the *precise* sequence of *every* variant of the TWEAK receptor that is recited in the claims. Thus, the Specification provides comprehensive structural information about the peptide sequences recited in the claims.

Furthermore, the Specification provides a *functional* description of each molecule. The Specification provides examples, both working and prophetic, of assays that can be used to determine whether a molecule (*e.g.*, a fragment or variant of the TWEAK receptor) binds to TWEAK. *See* the Specification at, for example, page 18, line 14 through page 24, line 31 and page 25, line 1 through page 26, line 29.

Thus, the Specification provides a comprehensive structural and functional description of each of the TWEAK receptor fragments and variants that are recited in the claims. Consequently, the Specification conveys to one of skill in the art that

Applicants were in possession of the claimed invention as of the filing date. Accordingly, Applicants respectfully request that the instant rejection be withdrawn.

CONCLUSION

Applicants believe that the application is now in condition for allowance. No new matter has been introduced. An early and favorable action on the merits is earnestly solicited. If a fee is required in connection with this paper, please charge Applicant's Deposit Account No. 09-0089 in the amount necessary to permit consideration of this amendment and response.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

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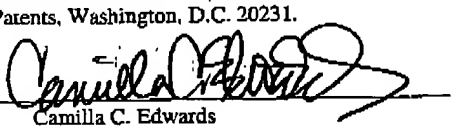
Date: 10/3/02 By: 
Camilla C. Edwards

APPENDIX A
U.S. Appl. Ser. No. 09/742,454
Marked-Up Copy of the Amended Claim

39. (Amended) A method of [modulating] inhibiting the binding of TWEAK to a TWEAK receptor in a mammal in need of such treatment, comprising administering to the mammal an inhibition-effective amount of a composition comprising a TWEAK receptor antagonist wherein the antagonist is selected from the group consisting of [: (a) a polypeptide comprising] a soluble TWEAK receptor [extracellular domain; and (b)] polypeptide that binds TWEAK, an antibody that binds [to] the TWEAK receptor [extracellular domain], an antisense nucleic acid, a triple helix forming nucleic acid, a peptide, and a small molecule.